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TECH CENTER 1600/2900 Atty. Docket No.: 8654/2072 PATENT  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Krissansen, et al.  
Serial No.: 10/014,887  
Filed: December 11, 2001  
Entitled: "Cancer Therapy"

Examiner: Not Yet Assigned  
Group Art Unit: 1615  
Conf. No.: 2382

**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8a**

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David J. Dykeman  
Name of Person Mailing Paper  
*David J. Dykeman*  
Signature of Person Mailing Paper

Commissioner for Patents  
Washington, D.C. 20231

**TRANSMITTAL LETTER**

Enclosed for filing in the above-identified patent application, please find the following documents:

1. Supplemental Information Disclosure Statement;
2. Form PTO-1449 citing 124 references;
3. Copies of 124 cited references; and
4. Return Post Card.

The Commissioner for Patents is hereby authorized to charge any additional fees or credit any overpayment in the total fees to Deposit Account No. 16-0085, Reference No. 8654/2072. A duplicate of this transmittal letter is enclosed for this purpose.

Date: January 22, 2003

Respectfully submitted,

*David J. Dykeman*  
Name: David J. Dykeman  
Registration No.: 46,678  
Customer No.: 29933  
Palmer & Dodge LLP  
111 Huntington Avenue  
Boston, MA 02199-7613  
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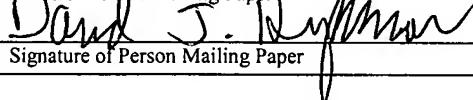
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**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT  
UNDER 37 CFR §§ 1.56, 1.97 AND 1.98**

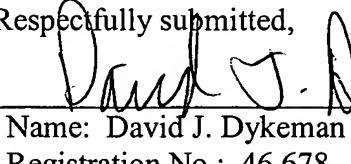
Dear Sir:

In accordance with the duty of disclosure under 37 CFR § 1.56, Applicant submits this Supplemental Information Disclosure Statement pursuant to 37 CFR §§ 1.97 and 1.98 in the above-identified application for consideration by the Patent Office. A listing of the cited documents is also enclosed, as well as, for the Examiner's convenience, copies of the documents in the list. Pursuant to CFR § 1.97(b)(3), because this Statement is being submitted before the first Office Action on the merits, no fee is required.

Applicant does not intend to represent that any of the documents submitted herein are material prior art to this invention or that the list represents an exhaustive search of documents related to this invention.

Applicant respectfully requests that the documents submitted herein be considered and made of record in this application.

Respectfully submitted,

  
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USPTO Form 1449  
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STATEMENT

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Filing Date: December 11, 2001

Group: 1615

## U.S. PATENT DOCUMENTS

Examiner Initial		Patent No.	Date	Name	Class	Subclass	Filing Date (if appropriate)
	1.	5,817,684	Oct. 6, 1998	Fleisch, et al.	514	381	
	2.	5,910,505	Jun. 8, 1999	Fleisch, et al.	514	381	
	3.	5,281,620	Jan. 25, 1994	Denny, et al.	514	455	

## FOREIGN PATENT DOCUMENTS

Examiner Initial		Document No.	Publication Date	Country	Class	Subclass	Translation	
							YES	NO
	4.	EP 0 743 064	20 Nov. 1996	European	A61K	31/19		
	5.	WO 94/23753	27 Oct. 1994	PCT	A61K	47/48		
	6.	WO 95/09621	13 April 1995	PCT	A61K	31/195		
	7.	WO 97/34482	23 Sept. 1997	PCT	A01N	43/00		
	8.	WO 98/25600	18 June 1988	PCT	A61K	31/19		
	9.	WO 98/42335	1 Oct. 1998	PCT	A61K	31/41		

## OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, etc.)

	10.	Wilson, W., Baguley B.; "Combination of the Antivascular Agent DMXAA with Radiation and Chemotherapy", <u>International Journal of Oncology, Biology and Physics</u> , volume 46, number 3, February 1, 2000, abstract 46, page 706.
	11.	Rustin, G.; "Vascular Targeting in the Clinic"; Abstract; <u>ICTR 2000: 1st Int'l Conference on Translational Research A.</u> , 2000.
	12.	Baguley, B.C. et al; "291 mechanisms of Tumor Blood Flow Inhibition by The Antitumour Drug DMXAA (5,6-dimethylxanthene-4-acetic acid)"; <u>Proceedings of the 11th NCI EORTC AACR Symposium; Copyright © 2000 Stichting NCI-EORTC Symposium on new drugs in cancer therapy</u> ; publ. By the AACR; Published as a Supplement to Clinical Cancer Research, vol 6, November 2000.
	13.	Chaplin, D.J., et al; "Antivascular approaches to solid tumor therapy; evaluation of tubulin binding agents"; <u>Proc. Annu. Meet. Am. Assoc. Cancer Res.</u> , March 1996, vol 37, #3009: 440-441 and Abstract.
	14.	Hornung R. L., et al; "Augmentation of Natural Killer Activity, Induction of IFN and Development Tumor Immunity During the Successful Treatment of Established Murine Renal Cancer Using Flavone Acetic Acid and IL-2"; <u>The Journal of Immunology</u> (1988) vol 141(10), pages 3671-3679.

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<b>U.S. DEPARTMENT OF COMMERCE</b> <b>Patent and Trademark Office</b> <b>TECH CENTER 1600/2900</b> <b>SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT</b>				Attorney Docket No. 8654/2072	Serial No. 10/014,887			
				Applicant(s): Krissansen, et al.				
				Filing Date: December 11, 2001		Group: 1615		
<b>U.S. PATENT DOCUMENTS</b>								
Examiner Initial		Patent No.	Date	Name	Class	Subclass	Filing Date (if appropriate)	
	121.	5,914,340	June 22, 1999	Fleisch et al.	514	381	March 13, 1998	
	122.	5,977,077	November 2, 1999	Winter et al.	514	23	March 20, 1996	
<b>FOREIGN PATENT DOCUMENTS</b>								
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	15.	WO 98/42332	1 Oct. 1998	PCT	A61K	31/35		
	16.	WO 98/42336	1 Oct. 1998	PCT	A61K	31/52		
	17.	WO 98/42337	1 Oct. 1998	PCT	A61K	31/41		
	18.	WO 98/42346	1 Oct. 1998	PCT	A61K	31/52		
	19.	WO 98/42650	1 Oct. 1998	PCT	C07C	63/04		
	20.	WO 00/10600 A2	2 March 2000	PCT	A61K	39/00		
	21.	WO 00/10600 A3	2 March 2000	PCT	A61K	39/00		
<b>OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, etc.)</b>								
	22.	Thomsen, L.L., et al.; "Nitric Oxide Production in endotoxin-resistant C3H/HeJ mice stimulated with flavone-8-acetic acid and xanthenone-4-acetic acid analogues"; <u>Biochem. Pharmacol.</u> , 43(11); pages 2401-2406; 1992.						
	23.	Lash, C.J., et al.; "Enhancement of the anti-tumor effects of the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) by combination with 5-hydroxytryptamine and bioreductive drugs"; <u>Br. J. Cancer</u> , 78(4), pages 439-445, 1998.						
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	25.	Pruijn, F.B., et al.; "Mechanisms of enhancement of the antitumor activity of melphalan by the tumor blood flow inhibitor 5, 6-dimethylxanthenone-4-acetic acid"; <u>Cancer Chemother. Pharmacol.</u> , 39(6), pages 541-546, 1997.						
	26.	Rewcastle, et al.; "Potential Antitumor Agents. 58. Synthesis and Structure-Activity Relationships of Substituted Xanthenone-4-acetic Acids Active against the Colon 38 Tumor in Vivo"; <u>J. Med. Chem.</u> , 32(4), pages 793-799, 1989.						
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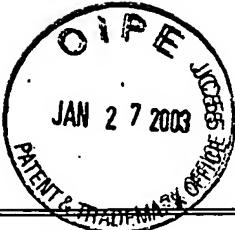


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	123.	5,998,454	December 7, 1999	Fleisch et al.	514	381	March 13, 1998
	124.	U.S. Patent Application Publication No. 2001/0027210	October 4, 2001	Wilson	514	455	January 31, 2001
<b>FOREIGN PATENT DOCUMENTS</b>							
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							YES
	27.	WO 00/16798	30 March 2000	PCT	A61K	38/28	
	28.	WO 01/34135 A2	17 May 2001	PCT	A61K	31/00	
	29.	WO 01/34137 A2	17 May 2001	PCT	A61K	31/00	
	30.	WO 01/34197 A2	17 May 2001	PCT	A61K	41/00	
	31.	WO 01/34198 A2	17 May 2001	PCT	A61K	41/00	
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	33.	WO 00/48591	24 Aug. 2000	PCT	A61K	31/198	
	34.	EP 0 584 001 A1	29 July 1993	European	A61K	31/335	
<b>OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, etc.)</b>							
	35.	Cliffe, S., et al.; "Combining bioreductive drugs (SR 4233 or SN 23862) with the vasoactive agents flavone acetic acid or 5, 6-dimethylxanthene acetic acid"; <i>Int. J. Radiation Oncology Biol. Phys.</i> , 29(2), pages 373-377, 1994.					
	36.	Phillips, R.M. "Inhibition of DT-diaphorase (NAD(P)H:quinone oxidoreductase, EC 1.6.99.2) by 5, 6-dimethylxanthene-4-acetic acid (DMXAA) and flavone-8-acetic acid (FAA): implications for bioreductive drug development"; <i>Biochem. Pharmacol.</i> , 58(2), pages 303-310, 1999.					
	37	Ching, L.-M., et al.; "Effect of thalidomide on tumor necrosis factor production and anti-tumor activity induced by 5, 6-dimethylxanthene-4-acetic acid"; <i>Br. J. Cancer</i> , 72(2), pages 339-343, 1995.					
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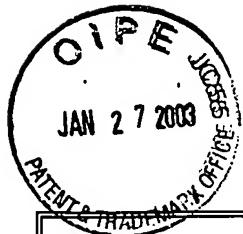
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	39.	EP 0 584 001 B1	14 May 1997	European	A61K	31/335		
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	41.	Ching, L.M., et al.; "Interaction of thalidomide, phthalimide analogues of thalidomide and pentoxyfylline with the antitumor agent 5, 6-dimethylxanthone-4-acetic acid: concomitant reduction of serum tumor necrosis factor-alpha and enhancement of antitumour activity"; <u>Br. J. Cancer.</u> , 78(3), pages 336-343, 1998.						
	42.	Kestell, P., et al.; "Modulation of the pharmacokinetics of the antitumor agent 5,6-dimethylxanthone-4-acetic acid (DMXAA) in mice by thalidomide"; <u>Cancer Chemother. Pharmacol.</u> , 46(2), pages 135-141, 2000.						
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	45.	Zwi, L.J., et al.; "Correlation between immune and vascular activities of xanthone acetic acid antitumor agents"; <u>Oncol. Res.</u> , 6(2), pages 79-85, 1994.						
	46.	Zhao, L., et al.; "Effects of the serotonin receptor antagonist cyproheptadine on the activity and pharmacokinetics of 5, 6-dimethylxanthone-4-acetic acid (DMXAA)"; <u>Cancer Chemother. Pharmacol.</u> , 47(6), pages 491-497, 2001.						
	47.	Futami, H., et al.; "Cytokine induction and therapeutic synergy with interleukin-2 against murine renal and colon cancers by xanthone-4-acetic acid derivatives"; <u>J. Immunother.</u> , 12(4), pages 247-255, 1992.						
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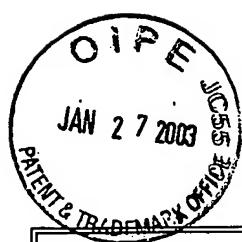
48.	Ching, L.M., et al.; "Interaction between endotoxin and the antitumour agent 5, 6-dimethylxanthene-4-acetic acid in the induction of tumor necrosis factor and haemorrhagic necrosis of colon 38 tumors"; <u>Cancer Chemother. Pharmacol.</u> , 35(2), pages 153-160, 1994.
49.	Ching, L.M., et al.; "Induction of intratumoral tumor necrosis factor (TNF) synthesis and hemorrhagic necrosis by 5, 6-dimethylxanthene-4-acetic acid (DMXAA) in TNF knockout mice"; <u>Cancer Res.</u> , 59(14), pages 3304-3307, 1999.
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51.	Baguley, et al.; "Evidence that the 5-hydroxytryptamine antagonist, cyproheptadine, modulates nitric oxide production in mice in response to flavone acetic acid, vinblastine and other agents"; <u>Biol. Nitric Oxide</u> , Proc. Int. Meet.; Meeting Date 1991, Volume 2, (1992); 222-224, 1991.
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54.	Fujii H, et al, "Vaccination with B7-18 tumor and anti-adhesion therapy with RGD pseudo-peptide (FC-336) efficiently induce anti-metastatic effect"; <u>Clinical &amp; Experimental Metastasis</u> , volume 16, pages 141-148, 1998.

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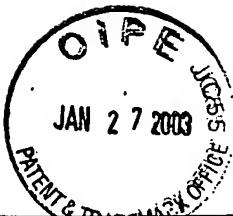
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55.	Zitvogel L., et al.; "Interleukin-12 and b7.1 co-stimulation co-operate in the induction of effective antitumor immunity and therapy of established tumor"; <u>Eur. J. Immunol.</u> , (1996), volume 26, pages 1335-1341.						
56.	Lissoni P., et al, "Neuroimmunotherapy of advanced solid neoplasms with single evening subcutaneous injection of low-dose interleukin-2 and melatonin Preliminary results"; <u>European Journal of Cancer</u> , (1993), volume 29A(2), pages 185-189.						
57.	Nawrocki S., and Mackiewicz A., "Genetically modified tumor vaccines-where we are today"; <u>Cancer Treatment Reviews</u> , (1999), volume 25, pages 29-46.						
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59.	"Combretastatin Update 1: In Ohio Phase 1 Trial, Some Tumors Respond, Patients Experience Vascular Stress"; <u>PSA Rising; Medical Pike Briefs; Headline Index: Clinical Trial Phase 1 Results</u> ; Nov. 8, 1999.						
60.	Zhou, et al.; "A difference between the rat and mouse in the pharmacokinetic interaction of 5, 6-dimethylxanthenone-4-acetic acid with thalidomide"; <u>Cancer Chemother Pharmacol</u> , (2001), 47(6), 541-544.						
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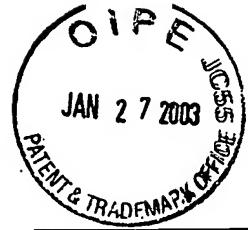
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61.	Zhou, et al.; "Determination of unbound concentration of the novel anti-tumor agent 5, 6-dimethylxanthenone-4-acetic acid in human plasma by ultrafiltration followed by high-performance liquid chromatography with fluorimetric detection"; <u>J. of Chromatography B</u> ; (2001) 757(2), 359-363.							
62.	Zhou, et al.; "Determination of the covalent adducts of the novel anti-cancer agent 5, 6-dimethylxanthenone-4-acetic acid in biological samples by high-performance liquid chromatography"; <u>J. of Chromatography B</u> ; (2001) 757: 343-348.							
63.	Zhou, et al.; "Reversible binding of the novel anti-tumor agent 5, 6-dimethylxanthenone-4-acetic acid to plasma proteins and its distribution into blood cells in various species"; <u>J. of Pharmacy and Pharmacology</u> ; (2001) 53(4), 463-471.							
64.	Zhou, et al.; "In vitro and in vivo kinetic interactions of the antitumour agent 5, 6-dimethylxanthenone-4-acetic acid with thalidomide and diclofenac"; <u>Cancer Chemother. Pharmacol.</u> ; (2001) 47(4), 319-326.							
65.	Cao, et al.; "Interferon-inducible Protein 10 Induction and Inhibition of Angiogenesis in Vivo by the Antitumor Agent 5, 6-Dimethylxanthenone-4-acetic Acid (DMXAA)"; <u>Cancer Research</u> ; (2001) 61(4), 1517-1521.							
66.	Murata, et al.; "Comparative effects of combretastatin A-4 disodium phosphate and 5, 6-dimethylxanthenone-4-acetic acid on blood perfusion in a murine tumor and normal tissues"; <u>Int. J. Radiat. Biol.</u> ; (2001) vol. 77, no. 2, 195-204.							
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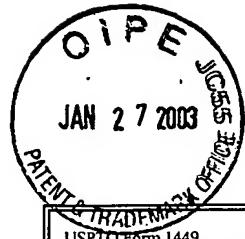
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Attorney Docket No.

8654/2072

Serial No.

10/014,887

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Filing Date: December 11, 2001

Group: 1615

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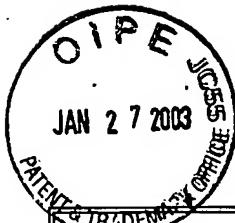
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